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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/781,980	02/14/2001	Michael Eisenhut	41443	9550

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EXAMINER	
SCHULTZ, JAMES	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 04/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/781,980	EISENHUT ET AL.	
	Examiner	Art Unit	
	J. D. Schultz, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8-13 and 15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8-13 and 15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

In response to a petition to revive filed 27 July 2004, which was approved on 29 November 2004, prosecution is hereby reopened. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 27 July 2004 has been entered.

Status of Application/Amendment/Claims

Applicant's response filed 27 July 2004 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 22 April 2003 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 103

Claims 1-6, 8-13 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nagy et al., in view of Lu et al., Taylor et al., Anderson et al., Khan, K et al., Godard, G et al., Ma, D. D. F (All of record), and Rajur et al. (Bioconjugate Chem. 1997, 8:935-940).

This rejection is based on the obviousness rejections of the previous Office action, but is amended somewhat to address applicants' claim amendments and thus supercedes previous obviousness rejections. One reference has been added to address the limitations whereby the somatostatin is conjugated to the oligonucleotide via a spacer to a base present on the oligonucleotide. This new grounds of rejection moots some of Applicants arguments; those that are considered relevant to the instant rejection are addressed following the instant rejection.

Claims 1-6, 8-13 and 15 are directed to an oligonucleotide conjugate comprising an oligonucleotide complexed at a base position via a spacer to a somatostatin analog wherein said oligo is complementary to a cellular mRNA transcript, wherein the oligonucleotide may be an oligodeoxyribonucleotide, or wherein the oligo phosphodiester bonds are at least partially replaced by phosphorothioate linkages, or wherein said oligo comprises a propanediol 3' end modification, or wherein said oligo contains an octreotide or octreotate somatostatin analog, or wherein said analog is covalently bonded to the 5' end, or wherein said analog is Tyr3 octreotate, or wherein said oligo targets mRNA or viral RNA or the coding region, or is 8 to 50 nucleotides long, or is 12 to 20 nucleotides long, or wherein said oligo targets bcl-2, or wherein said oligo is a peptide nucleic acid derivitive.

Nagy et al. teaches highly bioactive somatostatin analogs that are conjugated to cytotoxic compounds, wherein said somatostatin analogs are used to deliver said cytotoxic compounds to cause cell death in cells that express somatostatin receptors (see abstract, page 1796 para. 4, and pg. 1796, last para, to 1797). Nagy et al. does not teach said analogs conjugated to an oligonucleotide, modified or otherwise.

Lu et al. teaches compounds that are complexed to an oligodeoxyribonucleotide that is antisense to cellular transcripts. The compound of the conjugates of Lu et al. are used to target cells expressing receptors that recognize said compound, thereby delivering the attached oligodeoxyribonucleotide to specific cell types (see abstract, p. 273, para. 2, and discussion, particularly para. 1).

Ma, D. D. F teach bcl-2 phosphorothioate-modified antisense oligonucleotides conjugated to porphyrin to enhance targeting and cellular uptake.

Anderson et al. teach highly bioactive somatostatin analogs including octreotide, octreotate and Tyr3 Octreotate.

Taylor et al. teach that modification of antisense oligos, including the incorporation of phosphorothioate linkages into said oligos, confer a greater degree of resistance to nuclease-mediated-degradation (p. 562, para. 2 through p. 563), and pharmaceutical preparations. Taylor et al. also teach oligos that are modified at the base position, or that target mRNA or viral RNA or the coding region, wherein said oligos is 7-30 nucleotides long. Taylor et al. also teaches peptide nucleic acid (PNA) derivatives that are resistant to degradation.

Khan, K et al. teach 1-3 propanediol end modifications that confer nuclease resistance to oligonucleotides.

Godard, G et al. teach conjugates that are covalently bonded to the 5' position of oligonucleotides.

Rajur et al. teach that covalent conjugation of protein with oligonucleotide makes delivery of antisense molecules more efficient.

It would have been obvious for one of ordinary skill in the art to modify the antisense conjugate compounds of any of Nagy, Lu, Ma, Godard or Rajur et al. to comprise antisense to the bcl-2 gene as taught by Ma et al. with any of the somatostatin analogs of Anderson as taught by Nagy et al. It also would have been obvious to one of ordinary skill in the art to incorporate the nuclease resistance modifications and targeting features of Taylor et al., Khan et al., and Godard et al. into the antisense portion of such conjugates.

One would have been motivated to substitute the bcl-2 antisense from the bcl-2 antisense/porphyrin conjugate of Ma et al. or the antisense from the antisense/asialoglycoprotein conjugate of Lu et al. in place of doxorubicin from the somatostatin-analog /doxorubicin conjugates as taught by Nagy et al., because Nagy et al. teach that somatostatin conjugates can be used to deliver cytotoxic compounds to target cells that express the somatostatin receptor, which is abundantly expressed on many cancer cell types, and because Lu, Ma, and Rajur teach that conjugates comprising oligonucleotides and a targeting compound can more effectively deliver said oligonucleotide to its target.

One would have been motivated to use the somatostatin analog compounds of Anderson in such conjugates, because Nagy expressly teaches that such bioactive analogs of somatostatin can be used to deliver cytotoxic compounds, and because both Nagy and Anderson teach that such analogs have an increased half-life, which is desireable for longer bioactivity. Finally one would have been motivated to design nucleotide modifications into the instant oligonucleotide conjugates in the manner of Ma et al., Taylor et al., Khan et al., or Godard et al., because Taylor teach that oligos 7-30 nucleotides long are optimal for target access, that the coding region of mRNA's are preferred targeting sites, and because Ma expressly teaches phosphorothioate

modifications, and finally because Taylor et al., and Khan et al., teach that, base, PNA modifications, 1-3 propanediol modifications, improve bioactivity half-life and cellular uptake of antisense molecules, respectively. Godard et al., teaches 5' binding of conjugate to oligo, which comprises a substitutable design choice that was known in the art.

One of ordinary skill in the art would have had a reasonable expectation of success in formulating such conjugates, because Nagy and Lu et al. teach their methods of synthesis, because Rajur et al teaches how to conjugate a base of an oligonucleotide to a protein via a spacer, because bcl-2 antisense conjugates were known in the art via Ma, and because such nucleotide modifications are clearly described routinely performed by those of ordinary skill in the art. Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Response to Claim Rejections - 35 USC § 103

The instant rejection was set forth on the grounds that it would have been obvious for one of ordinary skill in the art to substitute an antisense compound as taught by Lu et al. (who teaches antisense conjugated to an asialoglycoprotein), or Ma (who teach a phosphorothioate bcl-2 antisense oligo conjugated to a poryphyrin in place of the cytotoxic compound of the somatostatin analog conjugates as taught by Nagy et al., as well as to incorporate phosphorothioate modifications into the antisense molecules of Lu et al. because Taylor et al. and Khan teach that such modifications improve bioactivity half-life and cellular uptake of antisense molecules.

Applicants have traversed the instant rejection by asserting that the instant combination of references does not teach all the elements of the claimed invention. In support of this, applicants have pointed to the presently claimed conjugate as being joined by a stable thioether bond, whereas the doxorubicin conjugation with the somatostatin of Nagy is performed by a peptide bond. Applicants conclude that Nagy would not inform one of skill how to prepare the stable thioether bond of the instant invention. In response to applicant's argument that the references fail to show how to make the stable thioether bond applicant's invention, it is noted that the features upon which applicant relies (i.e., the stable thioether bond) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Furthermore, this line of argumentation is addressed by the addition of the reference of Rajur et al. to the instant rejection, who teaches how to conjugate a base of an oligonucleotide to a protein via a spacer.

Applicants remaining arguments are dedicated to showing that the references do not teach the motivation to combine the references. According to Applicants, none of Nagy, Lu, or Taylor suggest or teach somatostatin analogs covalently coupled to antisense oligonucleotides. In response, it is acknowledged that none teach the instantly claimed compounds, or the rejection would have been made under 35 U.S.C. § 102, as opposed to the instant rejection which is maintained under 35 U.S.C. § 103(a). Insofar as the references do not suggest the instantly claimed compounds, this is not considered convincing because of the tremendous overlap of the references. Nagy teaches a protein (somatostatin)/doxorubicin conjugate, both Rajur and Lu teach an antisense/protein conjugate, and Ma teaches a bcl-2 antisense/poryphyrin conjugate.

Since protein/antisense conjugates were known and previously used, their very presence is a suggestion to make such compounds, particularly since such conjugates were taught as useful in increasing the efficiency of delivery. Since somatostatin was taught as an effective carrier protein by Nagy, and since bcl-2 antisense oligos were known in the art and targets a well-known oncogene, motivation to make this combination is considered to be expressly taught.

Applicants arguments that a reference of Wu, who was not cited, teaches away from the instant invention are not considered convincing. Applicants argue that Wu teaches that "covalent coupling might alter the DNA and preclude proper gene expression." However, Applicants are reminded that the instant invention has nothing to do with achieving proper gene expression. To the contrary, the antisense of the instant invention seeks to accomplish gene inhibition, and thus interfering with DNA expression may actually help accomplish applicants stated purpose. Furthermore, each of Nagy, Rajur et al., and Ma teach that covalently linked conjugates do not document such DNA expression problems.

Applicants cite several lines from Wu about the reason for using poly-L lysine, and not covalent linkages, for such DNA/protein conjugations, however, Wu is delivering a plasmid DNA that is comparatively very large (>3kb) and is to be translated, whereas the references cited herein are delivering antisense oligos that are usually less that 25 nucleobases, and are not transcribed. Therefore, DNA damage would not figure to be much of a concern in the case of an antisense molecule, since there is less of it to be damaged, and would not be required to be available for the complicated translational machinery. The fact that Wu teaches using proteins conjugated to target nucleic acid effectors to particular cells merely reinforces the obviousness of using conjugates to target a nucleic acid effector to a cell type. Thus, Lu is not considered to

teach away, since Lu and Wu both teach the value of such conjugates and since Nagy, Rajur and Ma teach such conjugates comprising covalent linkages.

No claims are allowed.

Conclusion

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz, Ph.D. whose telephone number is 571-272-0763. The examiner can normally be reached on 8:00-4:30 M-F.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

JD Schultz, PhD

JAMES SCHULTZ
PATENT EXAMINER